Urinary Phosphorus Excretion: Not what we have believed it to be?

Adamasco Cupisti[1], Maurizio Gallieni[2]

1. Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy;

2. Department of Clinical and Biomedical Sciences 'Luigi Sacco', University of Milan, Milan, Italy.

Human phosphate (P) homeostasis includes regulation of intestinal absorption from the diet, bone turn-over and renal excretion, and it is regulated by the combined actions of parathyroid hormone (PTH), 1,25-dihydroxy-vitamin D (calcitriol), and fibroblast growth factor 23 (FGF23); the renal phosphate threshold is the main determinant of serum P levels. In the case of significantly reduced GFR, the lower amount of ultra-filtered P strongly impairs its urine excretion capacity by PTH and FGF23. Thus, in chronic renal insufficiency patients a high phosphate load can cause P retention [1].

Under physiologic conditions, the whole-body balance of P is maintained by fine adjustments of urinary excretion to equal the net gastrointestinal absorption [2]. This is the reason why measurement of 24h urine P excretion has been considered a reliable indicator of net P absorption, which in turn is related to the quantity and type of P present in the diet. This concept has been also applied to patients with reduced renal function, provided a steady state condition.

In this issue of CJASN, Stremke and collaborators [3] question the role and reliability of a single 24h urine phosphate measurement as an indicator of dietary P intake and absorption in patients with CKD. In a controlled setting, a 2-week long balance study including eight patients with reduced renal function showed that 24-hour urine P measurement has wide day-to-day variability, and that the average of at least two 24h urine determinations is required for a reliable measurement. They also found that differences in urine P excretion reflected whole-body P retention and not differences in intestinal phosphorus absorption. In other words, for an individual patient, a low 24h urine P excretion may indicate a positive P balance rather than low net intestinal load, whereas a high 24h urine P excretion may be suggestive of a negative P balance rather than high net intestinal P absorption. However, the results and the conclusions of this elegant and interesting study must not be generalized to avoid the risk of misleading information. First, the conclusion cannot be applied to the general population with preserved kidney function, which efficiently maintains body P balance. In patients with renal insufficiency the potential reasons for heterogeneity in 24-hour urine P among individuals and day-to-day variation within individuals are numerous. Hence, as the Authors themselves appreciated, larger sample sizes are required to confirm the results.
Second, the potential differences in the bioavailability of P from various food sources could have contributed to the wide variability of phosphaturia, but the within-individuals' wide fluctuations in 24-hour urinary excretion both of P and of creatinine may be influenced by methodological problems, as well.
Third, equation-based predicted intakes both underestimated and overestimated the measured P intake by as much as 98% and 79%, respectively [3]. The lowest predicted P intake was less than 40

mg/day, and the highest was over 2800 mg/day: it cannot be excluded that such huge variations depended on inaccuracy of urine P determination.

The take-home message that would be derived from this study is very strong and needs confirmation in two different settings, clinical research and daily practice. In fact, conclusion that urinary P excretion is of no use, or even misleading, in the single patient or in observational studies may have an impact in the current nutritional management. In the everyday clinical practice, phosphaturia is considered a tool for estimation of effective dietary load, On the contrary, the Authors suggest that phosphaturia reflects P balance but not the intake; namely, low 24h urinary P excretion indicates P retention, while high P excretion reflects P depletion.

The Authors also speculates that reliability of 24h urine excretion can be even worse in the current clinical practice. However, in our experience, in a series of 67 stable outpatients affected by stage 3b-4 CKD in follow-up in our renal clinic, a significant direct relationship has been found between the protein catabolic rate, as a surrogate of protein intake, and phosphaturia ($r = 0.73$, $p<0.001$, personal observation) resulting approximately 11 mg of urine phosphorus per gram of protein intake. It is in accordance with the well known direct relationship between protein and phosphate content of a mixed diet (approximately 14 mg P per gram of protein). Therefore, phosphaturia strictly parallels dietary P load also in CKD patients.

The results of Stremke et al. are not well in keeping with other experience reported in the literature. For instance, Sigrist et al. [4] reported that low phosphate diet or P-binder therapy can reduce serum and urine P levels, as expected. Similarly, introducing a constant dietary P amount while changing from animal to plant origin, serum phosphate and phosphaturia decreased accordingly for the lower digestibility and bioavailability of P from vegetable sources [5]. In both these studies including CKD patients, the interpretation of the data is that lower P excretion was due to the expected lower net intestinal load of P (and not an indicator of P retention). Isakova et al [6] proved that dietary P restriction and the use of P binders lowered phosphaturia, also consistent with a decrease in P absorption.

Results of the study by Stremke et al are relevant because they suggest that likely 24h urine P excretion reflect not only dietary intake but also the changes in P balance, in renal insufficiency patients. The reported quite high variability implies that a single measurement may not give a reliable estimation of urine phosphate excretion. In any case, we should keep in mind that these results apply to patients with stage 3b-4 CKD.

Hence, the important role of 24h urine P excretion in subjects with preserved renal functions and in CKD patients who undergo dietary or pharmacological interventions remains still valid, provided steady state conditions.

Morimoto et al [7] reported that in subjects with preserved renal function the 24h urine P excretion can be used to estimate the dietary phosphorus intake and that it may be even superior to estimations based on weighed dietary records. Accordingly, Trautvetter et al. reported no difference between the estimated phosphorus intake from renal excretion and weighed dietary records, and concluded that 24 h urine collections should be used to assess the phosphorus intake. [8]
In this perspective, one of the conclusions of the study, namely the poor reliability of phosphaturia as an indicator of P intake/absorption, must be limited to the single measurement in cross-sectional population-based study including patients with chronic renal insufficiency.

The hypothesis that urine P excretion may be an inverse indicator of phosphate balance in patients in stable conditions remains difficult to accept, although we agree that 24h urine P excretion may not always be a reliable estimation of P dietary content. In fact, it should equal net intestinal absorption that is influenced by a number of factors other than dietary P content. Namely, P from plants sources is less digestible and hence less bioavailable than P from animal sources, while processed food with P-containing additives have the maximum potential bioavailability; concomitant use of active vitamin D and/or phosphate binders; cooking methods; industrial processing procedures [9].

Scanni et al [10] showed that even inorganic P administered by duodenal infusion is not totally found in urine: only 73% is excreted, while 100% is retrieved in urine when administered by iv infusion, demonstrating that in normal subjects the kidneys are able to excrete the effective P load, and that bioavailability is not only a function of digestibility [10].
In conclusion, 24h urine P measurement should still be mostly what we have believed it to be, namely an indicator of net P absorption, in steady state conditions. Though the relationships between P intake, bioavailability, absorption and urinary excretion are complex, we should not renounce to the precious information derived by repeated measurements of urinary P in the clinical setting. However, especially in 3b-4 CKD patients, a correct interpretation of the results is needed, considering that P balance can be influences by serum P, PTH and the dietetic and pharmacologic interventions adopted in the individual patient.

References

1. Vervloet MG, Sezer S, Massy ZA, Johansson L, Cozzolino M, Fouque D; ERA–EDTA Working Group on Chronic Kidney Disease–Mineral and Bone Disorders and the European Renal Nutrition Working Group: The role of phosphate in kidney disease. Nat Rev Nephrol 13:27-38, 2017

2. Blaine J, Chonchol M, Levi M. Renal control of calcium, phosphate, and magnesium homeostasis. Clin J Am Soc Nephrol 10:1257-1272, 2015

3. Stremke ER, McCabe LD, McCabe GP, Martin BR, Moe SM, Weaver CM, Peacock M, Hill Gallant KM: Twenty-four-hour urine phosphorus as a biomarker of dietary phosphorus intake and absorption in CKD. Clin JASN xx:xxx-xxx, 2018

4. Sigrist M, Tang M, Beaulieu M, Espino-Hernandez G, Er L, Djurdjev O, Levin A: Responsiveness of FGF23 and mineral metabolism to altered dietary phosphate intake in chronic kidney disease (CKD): results of a randomized trial. Nephrol Dial Transplant 28:161-169, 2013

5. Moorthi RN, Armstrong CL, Janda K, Ponsler-Sipes K, Asplin JR, Moe SM: The effect of a diet containing 70% protein from plants on mineral metabolism and musculoskeletal health in chronic kidney disease. Am J Nephrol, 40: 582-591, 2014

6. Isakova T, Gutierrez OM, Smith K, Epstein M, Keating LK, Juppner H, Wolf M: Pilot study of dietary phosphorus restriction and phosphorus binders to target fibroblast growth factor 23 in patients with chronic kidney disease. Nephrol Dial Transplant, 26: 584-591, 2011

7. Morimoto Y, Sakuma M, Ohta H, Suzuki A, Matsushita A, Umeda M, Ishikawa M, Taketani Y, Takeda E, Arai H: Estimate of dietary phosphorus intake using 24-h urine collection. J Clin Biochem Nutr 55: 62–66, 2014

8. Trautvetter U, Ditscheid B, Jahreis G, Glei M. Habitual Intakes, Food Sources and Excretions of Phosphorus and Calcium in Three German Study Collectives. Nutrients. 10:(2), 2018

9. Cupisti A, Kalantar-Zadeh K: Management of natural and added dietary phosphorus burden in kidney disease. Semin Nephrol 33:180-190, 2013

10. Scanni R, vonRotz M, Jehle S, Hulter HN, Krapf R: The human response to acute enteral and parenteral phosphate loads. J Am Soc Nephrol 25:2730-2739, 2014